Martin-Loeches *et al.*
Journal of Intensive Care (2026) 14:1
https://doi.org/10.1186/s40560-025-00836-5

Journal of Intensive Care

RESEARCH

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Management of endothelial dysfunction in septic shock: role of albumin administration

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Abstract

Sepsis is a significant global health issue, with high morbidity, mortality, and economic burden. Its definition has evolved, with the latest Sepsis-3 criteria emphasizing life-threatening organ dysfunction due to a dysregulated host response. Endothelial dysfunction plays a critical role in sepsis pathogenesis, characterized by increased permeability and inflammatory responses. Human serum albumin, the most abundant protein in the bloodstream, is essential for maintaining oncotic pressure and endothelial integrity. This narrative review provides an overview of endothelial changes during sepsis and their impact on organ damage. We also explore the role of albumin administration in managing endothelial dysfunction in sepsis and discuss the available preclinical and clinical evidence.

Keywords Sepsis, Endothelium, Albumin, Fluid resuscitation, Endothelial dysfunction

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Background

Sepsis is a systemic condition that affects nearly all organs and tissues [1]. The effective management of sepsis within the initial hours of diagnosis may be crucial for preventing organ failure and improving patient outcomes [2]. The endothelium, a thin layer of cells lining the interior surface of blood vessels, responds to inflammation and infection in a manner that may significantly damage vascular function and, secondarily, organ function. These responses include a phenotypic shift (i.e., proapoptotic, proinflammatory, proadhesive, and procoagulant), and activation of a "danger signaling" cascade in response to the presence of microbial toxins. The result of this process is damage to the glycocalyx and endothelial cell apoptosis. These, in turn, lead to an increased permeability to proteins and fluids, causing interstitial leakage, tissue edema, and organ failure [1, 3]. Consequently, the ability to reduce endothelial dysfunction may be an essential component for improved treatment of sepsis.

Human serum albumin, the most abundant protein in the bloodstream, is crucial not only for regulating oncotic pressure, but also for its non-oncotic roles, which include transporting substances, maintaining acid–base balance,

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and preserving endothelial integrity. These features make albumin a unique colloid, with distinct characteristics when compared to other plasma volume expanders [4]. Low serum albumin concentrations, common in critically ill patients, are linked to poorer outcomes, making its administration a consideration in these cases [5, 6]. Although therapeutic albumin has a proven safety record in various diseases, its use in critically ill patients remains debated and should be reserved for those with demonstrated benefits [5, 7, 8].

This narrative review focuses on the contribution of endothelial dysfunction to sepsis and the role of albumin administration in its management. By integrating insights from basic science, preclinical studies, clinical data, and ongoing investigations this format allows for a broad synthesis of current knowledge. However, we acknowledge the inherent limitations of a narrative approach, including potential susceptibility to selection bias.

Sepsis: definition and current strategies

Definition

The definition of sepsis has evolved significantly since the first international consensus in 1991 [9]. Initially, sepsis was defined as a systemic inflammatory response syndrome. Over time, it changed to the identification and development of organ dysfunction [10]. The latest update by the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) in 2016 redefined sepsis as a life-threatening organ dysfunction caused by a dysregulated host response to an infection [11]. Furthermore, this update also eliminated the term "severe sepsis", redefined septic shock to include persistent low blood pressure requiring vasopressors with elevated serum lactate concentrations and introduced the use of Sequential (or Sepsis-related) Organ Failure Assessment (SOFA) and the "quick" (q)SOFA criteria to identify patients at risk of organ failure and deterioration [11].

Epidemiology

Sepsis remains a major healthcare problem worldwide, impacting millions of people each year and resulting in significant morbidity and mortality [2]. In the United States, at least 1.7 million adults develop sepsis annually, with nearly 265,000 fatalities [1]. In Europe, the incidence is even higher, with over 3.4 million cases per year and approximately 700,000 deaths during hospitalization [1]. Globally, sepsis affected an estimated 48.9 million people in 2017, accounting for 19.7% of all deaths [12].

The economic burden of sepsis is also substantial, with costs exceeding 24 billion dollars per year in developed countries [3]. This underlines the importance of early identification and treatment of sepsis. The evolution of our understanding of sepsis has driven the development of current treatment strategies.

Treatment strategies

A study of patients with severe community-acquired pneumonia, a common cause of sepsis, who received appropriate antibiotic therapy and management of comorbid medical conditions, found a mortality rate of 22–32%, reaching 45–50% for those developing septic shock [13]. The mortality rates indicate that antibiotics alone are not sufficient to prevent death in severe infections. Indeed, Seymour et al. identified four novel clinical sepsis phenotypes (α, β, γ, and δ), each with different demographics, laboratory values, and organ dysfunction patterns [14]. These phenotypes correlated with biomarkers of host-response patterns and clinical outcomes, and simulations suggested that these phenotypes explain at least some part of the heterogeneity of treatment effects [14]. Other phenotypes have also been promulgated, although consensus around their optimal clustering and therapeutic import has yet to emerge [15].

Due to its life-threatening nature, the management of sepsis involves ongoing resuscitation and stabilization even while the precipitating infection and organisms may remain obscure. The supportive management aims to treat pathophysiological consequences common to all cases of sepsis, while buying time to enable definitive diagnoses to be made. This initial management can be standardized, with this approach improving outcomes for patients [16], but there remains considerable scope for correctly targeted, non-specific therapies to further improve outcomes.

The role of the endothelium and endothelial damage

The role of healthy endothelium

The endothelium performs a dual role and interacts with blood components in a bi-directional fashion, functioning as both receptor and transmitter of signals between tissues and blood. Additionally, the endothelium regulates vascular permeability by maintaining tight, gap, and adherence junctions. These junctions, along with the protective endothelial glycocalyx layer, limit cell migration and capillary leakage, while also maintaining an anti-inflammatory and anti-thrombotic environment. Ultimately, these functions assist in the prevention of clot formation, thereby ensuring systemic perfusion (Fig. 1A) [3].

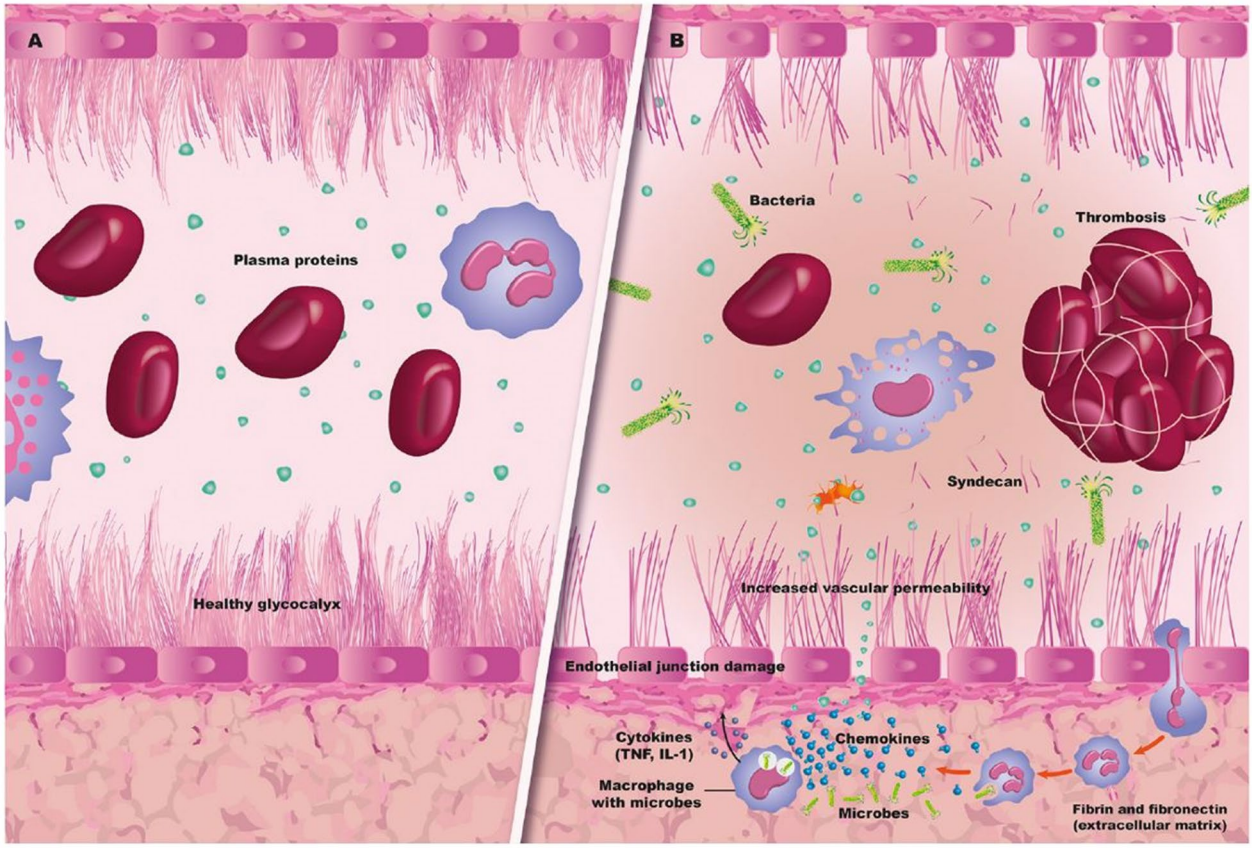

Fig. 1 Sepsis and endothelium. **A** A healthy blood vessel featuring an intact glycocalyx and endothelium. **B** Endothelial damage associated with sepsis, characterized by bacteremia, thrombus formation, capillary leakage, and leukocyte migration. (Reprinted from Fernández-Sarmiento et al., *Front Pediatr*. 2022;10:828,968. Licensed under CC BY http://creativecommons.org/licenses/by/4.0/. No changes were made to the original figure.)

The role of endothelial cells in sepsis: immune response and coagulation activation

The endothelium plays a crucial role both in the development and perpetuation of organ failure during sepsis, through immune response enhancement and coagulation system activation (Fig. 1B) [1]. During sepsis, endothelial cells contribute to end-organ damage through a cascade of events that triggers both initial organ activation and late organ dysfunction [3]. Endothelial cells serve as both targets and sources of inflammatory mediators, bridging local and systemic immune responses [1]. In reaction to the presence of cytokines (e.g., TNFα, INFγ), the endothelium expresses adhesion molecules and produces inflammatory cytokines, vasoactive substances, and chemoattractants, shifting from an anticoagulant to a procoagulant state [1, 3, 17].

Under physiological conditions, the endothelial glycocalyx is substantially thicker than membrane-bound selectins (typically ~ 500 nm vs. 20–40 nm), forming a physical and functional barrier that prevents leukocyte adhesion. When the glycocalyx is shed, selectins become exposed, initiating leukocyte rolling and firm adhesion to the endothelial surface [18].

Key endothelial cell adhesion molecules involved in leukocyte–endothelial interactions during sepsis include Intracellular Adhesion Molecule 1 (ICAM-1), Vascular Cell Adhesion Molecule 1 (VCAM-1), and selectins (E-, L-, and P-selectin). Vascular Endothelial Growth Factor (VEGF), although not a classical adhesion molecule, contributes to endothelial activation and permeability by inducing the expression of adhesion molecules such as ICAM-1 and VCAM-1 [19]. Patients with multiple organ failure (MOF) exhibit significantly higher levels of VCAM-1 and ICAM-1 compared to those with single organ failure [20]. Elevated serum ICAM-1 levels are linked to the development of MOF, while increased VCAM-1 levels are associated with both MOF and in-hospital mortality [20]. Given the central role of endothelial activation in sepsis, there is growing interest in therapeutic strategies that may modulate this response. Albumin, beyond its oncotic properties, has been shown in vitro to inhibit TNF-alpha-induced VCAM expression

in human aortic endothelial cells. These findings suggest a potential immunomodulatory effect of albumin on endothelial activation. However, the effects of albumin on adhesion molecules remain complex and need further investigation in vivo and in clinical settings [20].

Additionally, the decompartmentalization of the inflammatory response mediated by endothelial cells plays a pivotal role in systemic inflammation. The loss of endothelial barrier function is a critical aspect in the development of systemic inflammation, as it leads to increased vascular permeability and the uncontrolled spread of inflammatory mediators. This barrier dysfunction exacerbates the inflammatory response, contributing to the progression of organ failure during sepsis [21].

Endothelial permeability and the glycocalyx in sepsis

Sepsis is characterized by a significant increase in endothelial permeability, which disrupts tissue fluid homeostasis and impairs normal organ function [22, 23]. One proposed mechanism is damage to the endothelial glycocalyx, a critical regulator of barrier integrity. The glycocalyx, located between the blood and vessel wall, plays a vital role in maintaining endothelial barrier function, in part through mechanotransduction [24, 25]. Damage to the glycocalyx is caused by reactive oxygen species and bacterial components [1]. This damage, along with the presence of inflammatory cytokines, leads to the disruption of endothelial tight junctions, adherence junctions, and gap junctions, thereby increasing endothelial permeability [1].

In addition, shedding of the glycocalyx exposes the endothelial cells to leukocyte and platelet adhesion, further exacerbating inflammation and activating the clotting cascade (Fig. 1B) [3, 26]. The result of these processes is capillary leak, edema, and further loss of endothelial barrier function [3].

While damage to the endothelial glycocalyx has been proposed as a key contributor to increased vascular permeability in sepsis, this relationship remains controversial. Some studies questioned whether glycocalyx degradation directly leads to increased permeability in vivo, suggesting that other mechanisms may be equally or more relevant [27]. These findings underscore the complexity of endothelial barrier regulation and the need for further research.

Resuscitation

Fluid resuscitation is a vital, life-saving intervention in patients with sepsis [28]. While fluid resuscitation is often necessary, it must be handled judiciously to avoid further complications. The lungs, with their delicate and extensive network of endothelial surfaces, are particularly at risk [29]. Sepsis, from both pulmonary and extra-pulmonary sources, is the leading cause of acute respiratory distress syndrome (ARDS) [29]. The endothelial damage that is seen in ARDS and sepsis combines with accumulated fluid to drive both hydrostatic and inflammatory edema, with consequent adverse outcomes [28, 29]. Indeed, a higher cumulative fluid balance is associated with increased mortality risk, longer mechanical ventilation times, and extended intensive care unit (ICU) stays, highlighting the potential importance of restrictive fluid therapy in managing patients with or at risk of ARDS [28].

Albumin and resuscitation

In addition to the standard of care with conservative fluid therapy, multiple therapies may be used for sepsis [29]. One such treatment is albumin.

Albumin has numerous physiological functions, including oncotic properties (regulation of fluid distribution), and non-oncotic ones [30]. Some of these non-oncotic properties include antioxidant activity, binding capacity to facilitate transport and metabolism of intrinsic and extrinsic molecules, modulation of immunological and inflammatory responses, endothelial stabilization, and regulation of platelet function and coagulation (Fig. 2) [30]. Many of these functions have the potential to modify pathophysiological pathways in sepsis.

Preclinical evidence

The effects of human albumin on endothelial glycocalyx and microcirculation have been assessed in in vitro, in vivo, and ex vivo studies [31]. These studies examined, for example, the ability of albumin to preserve the integrity of the glycocalyx, partially restore compromised vascular permeability, exert anti-inflammatory and antioxidant effects, enhance microcirculatory function and stabilize hemodynamics following hemorrhagic shock or endotoxemia, as well as to serve as an efficient plasma volume expander [31].

More specifically, in vitro and in vivo models show that albumin contributes to the maintenance of vascular permeability by delivering sphingosine-1-phosphate to the endothelium, which suppresses metalloproteinase activity and reduces glycocalyx degradation [32–34]. It also scavenges reactive oxygen species and modulates cytokine production, exerting antioxidant and anti-inflammatory effects [4, 35, 36]. In animal models of hemorrhagic shock and endotoxemia, albumin infusion partially restored glycocalyx thickness, improved microcirculatory perfusion, and stabilized vascular permeability [37–39]. For example, in rats subjected to hemorrhagic shock, albumin reduced plasma syndecan-1 levels and improved leukocyte–endothelium interactions [39], while in endotoxemic mice, it

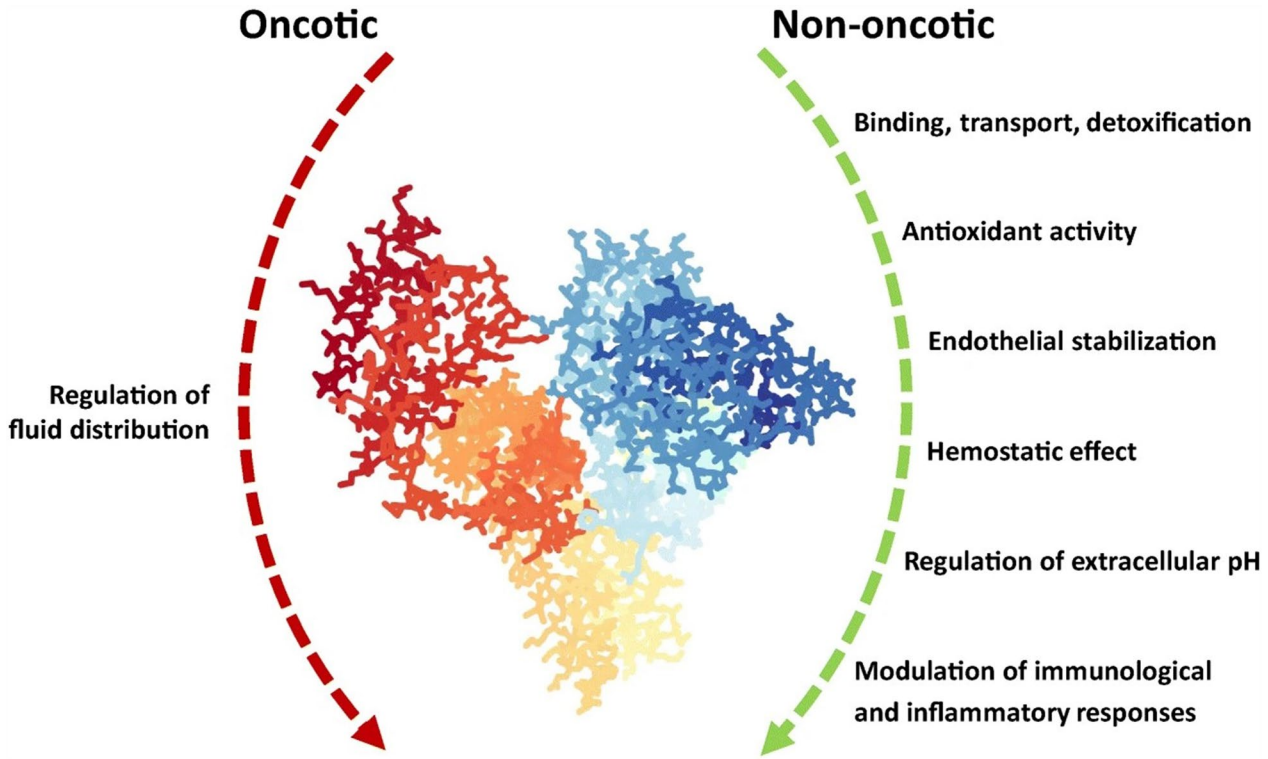

Fig. 2 Albumin properties. (Reprinted from Tufoni et al., *Current Hepatology Reports*, 2020;19 (3):147–158. Licensed under CC BY 4.0 http://creativecommons.org/licenses/by/4.0/. No changes were made to the original figure.)

increased survival and enhanced perfused vessel density [38]. Albumin has also shown superior efficacy compared to crystalloids or synthetic colloids in preventing fluid extravasation and maintaining microvascular integrity in ischemia–reperfusion models [40, 41].

A summary of preclinical studies evaluating the mechanisms of action of albumin in sepsis is presented in Table 1.

Potential risks of albumin therapy in sepsis

While albumin administration offers several potential benefits in sepsis, including endothelial stabilization and improved tissue perfusion, its use in conditions of high vascular permeability warrants careful consideration due to the risk of extravasation and tissue edema. However, despite the increased capillary permeability observed in sepsis, randomized controlled trials (RCTs) have shown that serum albumin levels increase in patients receiving albumin therapy [42–44], suggesting that not all exogenous albumin leaks into the interstitial space.

Sepsis is characterized by profound endothelial dysfunction and glycocalyx degradation, which increase capillary permeability and allow plasma proteins such as albumin to leak into the interstitial space. This leakage

Table 1 Preclinical models used to study the albumin mechanism of action. (Adapted from Aldecoa et al.)

Preclinical model	Main findings
Rat perfused venular microvessel	Primary MoA of albumin in maintaining vascular permeability is release of S1P from red blood cells
Rat experimentally induced hypovolemic shock	Albumin administration partially restored endothelial glycocalyx thickness and microvascular permeability
In vitro human uterine vein endothelial cells exposed to LPS and TNF-α	Human serum albumin (4%) inhibited inflammatory and oxidative stress pathways induced by endotoxins
In vitro artificial semipermeable membrane	Albumin decreased water permeability of ultrafiltration membranes in a concentration dependent manner

MoA mechanism of action, *S1P* sphingosine-1-phosphate

may paradoxically worsen tissue edema by raising interstitial oncotic pressure, impairing oxygen diffusion and organ function [45–49].

Experimental and clinical studies have demonstrated that elevated levels of inflammatory mediators (e.g., TNF-α, IL-6, VEGF) and markers of glycocalyx damage (e.g., syndecan-1) correlate with increased vascular permeability and albumin extravasation [45, 48, 50, 51].

In patients with advanced cirrhosis and sepsis, albumin infusion has been associated with extracellular fluid overload and failure to correct hypovolemia, particularly in the presence of impaired lymphatic drainage [47].

Moreover, hypoalbuminemia in sepsis is not only a marker of disease severity but also reflects ongoing albumin loss into the interstitial space, contributing to hypovolemia and edema [52, 53].

Although albumin may improve microcirculatory function and modulate inflammation [4, 54, 55], randomized trials have not consistently demonstrated a survival benefit compared to crystalloids [42, 56]. Therefore, a balanced approach is essential, weighing both the potential benefits and risks of albumin therapy in septic patients with increased vascular permeability. Future research should aim to identify patient subgroups most likely to benefit from albumin, and to develop strategies that mitigate the risk of extravasation, such as targeting glycocalyx preservation or endothelial repair [54].

Clinical evidence: mortality outcomes

Although basic science suggests that albumin may protect the glycocalyx and improve endothelial function, its potential impact on mortality in patients with sepsis or septic shock remains inconclusive. Large RCTs (SAFE, ALBIOS, and EARSS) have compared albumin with crystalloids in critically ill patients with sepsis. While these trials suggested a trend toward reduced 28-day mortality with albumin, particularly in subgroups with septic shock, none demonstrated a statistically significant overall survival benefit [42, 43, 57]. Table 2 presents a summary of these trials [42, 43, 57–60]. The heterogeneity in outcomes across these trials may be partly explained by differences in study design, albumin concentration, administration protocols, and patient populations. For instance, the SAFE trial used 4% albumin and allowed clinicians to determine dosing, while ALBIOS and EARSS employed 20% albumin with structured administration protocols based on serum albumin levels or fixed dosing schedules. Moreover, patient selection varied: SAFE included a broad ICU population with severe sepsis, ALBIOS focused on patients with septic shock and severe sepsis, and EARSS targeted early resuscitation [42, 43, 57–60]. These methodological differences likely influenced fluid balance, timing of intervention, and therapeutic response, contributing to the inconsistent findings. Understanding these nuances is essential for interpreting trial results and identifying subgroups that may benefit most from albumin therapy.

In addition to the main SAFE trial, a post hoc follow-up study, the SAFE–TBI study, specifically evaluated outcomes in patients with traumatic brain injury (TBI). Among 460 patients with TBI, those resuscitated with 4% albumin had significantly higher mortality at 24 months compared to those receiving saline (33.2% vs. 20.4%; RR 1.63; 95% CI 1.17–2.26; $P=0.003$). In patients with severe

Table 2 Study design and mortality rates of the main clinical studies on albumin in ICU

	SAFE [57, 58]	ALBIOS [42, 60]	EARSS [43, 59]
Albumin type	4%	20%	20%
Patients' characteristics	Adult patients admitted at the ICU with severe sepsis	Adult patients admitted at the ICU with severe sepsis or septic shock	Adult patients admitted at the ICU with septic shock
Arms	Alb 4% vs saline	Alb 20% vs saline	Alb 20% vs saline
Intervention starting time	Not specified	3 h	Not specified
Loading dose	No	300 ml alb 20% in 3 h	No
Albumin administration protocol	The treating clinicians determined the amount and rate of fluid administration	• < 25 g/L: 300 mL of alb 20% in 2 h • 25 – 30 g/L: 200 mL of alb 20% in 2 h • ≥ 30 g/L: No administration	100 mL of alb 20% every 8 h
Treatment duration	28 days or ICU discharge (whichever came first)	28 days or ICU discharge (whichever came first)	3 days
Number of patients	603 alb arm 615 saline arm	895 alb arm 900 saline arm	399 alb arm 393 saline arm
Mortality rate at 28 days, albumin group	30.7%	31.8%	24.1%
Mortality rate at 28 days, saline group	35.3%	32.0%	26.3%

Alb albumin, *ALBIOS* Albumin Italian Outcome Sepsis, *EARSS* Early Albumin Resuscitation during Septic Shock, *ICU* intensive care unit, *SAFE* Saline versus Albumin Fluid Evaluation

TBI, mortality was even higher in the albumin group (41.8% vs. 22.2%; RR 1.88; 95% CI 1.31–2.70; $P<0.001$). These findings suggest that albumin may be harmful in the acute resuscitation of patients with severe TBI and support the preferential use of saline in this population [61]. While the SAFE–TBI study linked hypotonic 4% albumin to increased intracranial pressure (ICP) and higher mortality in patients with TBI, recent commentary has questioned the generalizability of these findings. Vincent et al. (2025) argue that the observed harm may be attributable to the hypotonicity of the albumin formulation used (278 mOsm/kg), rather than to albumin itself. Preclinical data suggest that isotonic or hyperoncotic albumin (≥300 mOsm/kg) may reduce ICP and improve outcomes. These insights highlight the need to re-evaluate albumin use in TBI, particularly with hyperoncotic formulations, and caution against broad contraindications based solely on hypotonic albumin [62].

Several metanalyses have synthesized these findings. A 2011 meta-analysis initially reported a mortality benefit with albumin [63], but its conclusions were later undermined by the inclusion of retracted studies and the dominance of the SAFE trial [64–70]. Subsequent analyses in 2014 showed a possible reduction in 90-day mortality in the sub-group of patients with septic shock (odds ratio 0.81; 95% CI 0.67–0.97; $P=0.03$), though no benefit was observed in the broader population with severe sepsis [71]. Another meta-analysis published the same year found no significant difference in all-cause mortality, although sensitivity analyses excluding high-risk-of-bias trials suggested a trend favoring albumin (relative risk 0.93; 95% CI 0.86–1.01; $P=0.07$) [72].

A pooled analysis by Wiedermann and Ioannidis reported a modest mortality reduction across the three major RCTs (relative risk 0.92; 95% CI 0.84–1.00; $P=0.046$) [73]. More recently, a 2024 meta-analysis focusing on hyperoncotic (20%) albumin found weak evidence of short-term mortality benefit in patients with septic shock, but minimal support for its use in sepsis overall [56].

Clinical evidence: administered fluid volume

One of the issues raised in relation to trials comparing resuscitation with albumin to other fluids, was the need to decrease the volume of administered fluids with albumin to create a fair comparison. Illustrating this issue are the results of an RCT comparing resuscitation volume requirements, fluid balance, and biochemical and physiological efficacy of 20% albumin versus 4–5% albumin in ICU patients [74]. When compared to 4–5% albumin, 20% albumin reduced resuscitation fluid volumes and minimized fluid accumulation, thereby mitigating the adverse events of a positive fluid balance [74]. Notably, there was no significant difference in the total volume of resuscitation fluid administered between patients with and without sepsis. Moreover, the use of 20% albumin did not adversely affect kidney function, addressing concerns that rapid administration of 20% albumin might induce a hyperoncotic state, decrease glomerular filtration rate, and result in insufficient intravascular volume expansion [74]. Consequently, the administration of a low volume of fluid with 20% albumin to critically ill patients is feasible, and appears safe, potentially allowing effective resuscitation with smaller fluid volumes.

A retrospective, observational, database-based study evaluated the effects of albumin in septic patients with coronary heart disease, who may require cautious use of fluids [75]. All-cause 28-day mortality was significantly higher among patients who did not receive albumin compared with patients who did receive albumin [75]. However, no benefit was observed in 90-day all-cause mortality, or in 28-day and 90-day cardiovascular mortality [75]. These findings remained stable across adjustments—for age and sex and for multiple variables, including baseline serum albumin [75].

Clinical evidence: effects on organ support and perfusion

In addition to its potential impact on mortality, albumin administration in patients with septic shock has been studied in relation to other clinically relevant outcomes. One area of interest is renal function. Albumin may help preserve kidney function by maintaining oncotic pressure and limiting fluid overload, which could reduce the risk of acute kidney injury and the need for renal replacement therapy (RRT). Some studies support this protective effect [56, 76, 77], although others have not found significant differences in RRT use when compared with crystalloids [42, 57].

Regarding respiratory support, a study noted that patients who received albumin required significantly less mechanical ventilation compared to those who did not [78]. However, others have not found significant differences in the duration of mechanical ventilation when compared to crystalloids [42, 57].

Another important consideration is the need for vasopressor support. While the duration and use of vasopressor do not appear to be consistently reduced with albumin administration in some studies [57, 79], other evidence shows a significantly shorter time to discontinuation of vasopressors in patients receiving albumin compared to those treated with crystalloids [42]. Additional studies have proposed that albumin may enhance microcirculatory function and preserve endothelial integrity, which could contribute to improved hemodynamic stability even in the absence of a clear reduction in vasopressor duration [79, 80].

More promising findings have emerged regarding the effects of albumin on microcirculation and tissue perfusion. Albumin has been shown to improve microvascular density and activity in patients with fluid-responsive septic shock [79]. A prospective, proof-of-concept trial investigated the effects of albumin versus saline administration on sepsis-related peripheral tissue hypoperfusion in resuscitated sepsis patients, using a variety of markers, including mottling and fingertip capillary refill time, to assess tissue perfusion [80]. Despite the inclusion of a small sample of patients (21 with albumin and 29 with saline), this trial provided intriguing insights into hypoperfusion. Capillary refill within < 3 s, a lower fingertip capillary refill time, and a decrease in mottling were more frequent and pronounced one hour after administration of albumin compared to saline [80]. These beneficial effects on peripheral tissue perfusion were sustained at four hours, with a trend toward higher urinary output in the albumin group [80]. Additionally, arterial lactate concentrations significantly decreased after treatment with albumin but remained unchanged with saline [80]. These findings lead to the conclusion that resuscitation with albumin may improve tissue hypoperfusion more than resuscitation with saline and suggest that albumin could potentially increase both peripheral and global tissue perfusion [80].

Albumin *concentration*

A recent meta-analysis examined the efficacy of different albumin concentrations for reducing mortality rates in patients with sepsis and septic shock [81]. Human albumin solutions with a concentration either similar to plasma (4–5%), or more concentrated (20%), were compared to crystalloids [81]. Overall eight RCTs including 5124 patients with sepsis and 3482 patients with septic shock were assessed [81]. When compared to crystalloids, albumin, particularly at a concentration of 20%, significantly reduced 90-day mortality in patients with septic shock [81]. Both 4–5% and 20% albumin demonstrated a trend toward improved outcomes in septic patients, with 20% albumin showing the most substantial benefit [81]. Patients with septic shock constituted a subgroup of populations of these studies and no head-to-head studies of 4–5% vs 20% have been conducted at the time of this analysis. This analysis indicates the potential benefit of 20% albumin, particularly for decreasing 90-day mortality among patients with septic shock, but there is a need for further proof of such benefit, as well as for evidence of a long-term effect on survival and quality of life.

The limitations of albumin research and costs

Evidence for albumin use in sepsis has limitations due to variations in study design, patient populations, and treatment protocols leading to heterogeneous findings [42, 43, 57, 70]. Some studies suggest a survival benefit, particularly at higher concentrations, while other studies show no significant advantage. This underscores the need for targeted research to identify patient subgroups that may benefit most.

The cost-effectiveness of albumin remains debated, as it is significantly more expensive than crystalloids. Economic evaluations vary by country: in the United States (US), Farrugia et al. reported an incremental cost–effectiveness ratio (ICER) of 1,285 US dollars (USD), well below the cost-effectiveness threshold (50,000–150,000 USD) [82]. In France, Guidet et al. found costs per life-year gained (LYG) of 974 Euros (EUR) and 617 EUR, both below the European threshold (20,000–30,000 EUR) [83, 84]. In contrast, Tigabu et al. in Iran found an ICER of 5,500 USD, exceeding the national threshold (5,219 USD) [85]. These differences likely reflect variations in economic conditions and healthcare systems.

Although several economic evaluations have suggested that albumin may be cost-effective in specific healthcare settings—such as the EMAISS and COASST studies in Europe or the analysis by Farrugia et al. in the United States—these findings are highly context-dependent. They rely on assumptions about pricing, reimbursement policies, and clinical practice patterns that may not be generalizable. Importantly, the lack of consistent survival benefit in major RCTs raises questions about the justification for routine use of albumin, particularly in resource-limited environments. Future cost-effectiveness analyses should incorporate not only mortality outcomes but also patient-centered endpoints such as duration of organ support, ICU length of stay, and long-term quality of life, to better assess the value of albumin therapy in sepsis. In this regard, two recent economic evaluations in patients with cirrhosis and ascites—one in Spain and another in the UK—provide relevant examples of how albumin's value has been assessed based on its impact on disease-related complications rather than mortality alone [86, 87]. Although these studies focus on cirrhosis rather than sepsis, they illustrate how albumin may offset its acquisition cost by preventing high-cost complications in conditions characterized by increased vascular permeability. These findings support the need for context-specific cost-effectiveness analyses when evaluating albumin therapy in critically ill patients.

Guidelines and ongoing studies

The evolution of international guidelines for the management of sepsis and septic shock reflects a growing body of evidence regarding the use of albumin in this condition. In the 2016 Surviving Sepsis Campaign guidelines, a weak recommendation to use albumin in addition to crystalloids for initial resuscitation and subsequent

intravascular volume replacement in patients with sepsis and septic shock was made with caution, citing low quality of evidence [88]. In the subsequent 2021 Surviving Sepsis Campaign guidelines the weak recommendation regarding albumin was made with slightly more assertion, suggesting that albumin be used in patients who received large volumes of crystalloids rather than continued use of crystalloids alone [2]. This recommendation was based on moderate quality of evidence, suggesting the potential benefits of albumin in such clinical scenarios [2].

At least three ongoing trials, ARISS, ALBIOSS-BAL, and SWIPE2, are currently investigating the efficacy of albumin in the management of septic shock (Table 3). In Germany, the ARISS (Albumin Replacement therapy In Septic Shock) trial (NCT03869385), employs a prospective, multicenter, parallel-grouped, open-label, interventional RCT design [89, 90]. This Phase 3 trial allocates patients to either albumin or crystalloids, with the primary outcome being 90-day mortality [89, 90]. The ARISS trial was initially designed to include 1662 patients. However, due to sustained low inclusion rates, the trial was terminated prematurely and actually included 440 patients [89, 90]. Preliminary results did not demonstrate a statistically significant reduction in mortality with albumin therapy compared to crystalloids. However, trends suggested a potential benefit of albumin, and it is possible that, had the original sample size been reached, a statistically significant difference might have emerged. Additionally, subgroup analyses may provide further insights [89]. These findings suggest that while albumin may offer physiological benefits, its impact on survival remains uncertain, reinforcing the need for targeted approaches and further investigation. The early termination of the ARISS trial due to slow recruitment raises important considerations for future research. One possible explanation is a lack of clinical equipoise among treating physicians regarding the effectiveness of albumin in septic shock, potentially influenced by prior inconclusive trial results and variability in clinical practice. This hesitation may reflect uncertainty about the therapeutic value of albumin outside specific subgroups and underscores the need for clearer patient stratification and more targeted endpoints in future studies. Additionally, it highlights the importance of designing trials that are both feasible and aligned with current clinical decision-making to ensure adequate enrollment and relevance.

In Italy, the ALBIOSS-BAL (ALBumin Italian Outcome Septic Shock BALANCED Trial; NCT03654001) is a 2-by-2, factorial, open-label, multicenter, RCT with plans to recruit 1252 patients [91]. This Phase 3 trial examines four allocation arms: albumin + balanced crystalloid solution, albumin + normal saline, balanced crystalloid solution, and normal saline [91]. The co-primary outcomes for ALBIOSS-BAL are 90-day mortality and the incidence of new acute kidney injury cases [91].

The SWIPE 2 (Strong Albumin Solutions in Patients With Septic Shock; NCT05208242) trial is being carried out in the United Kingdom and involves 50 patients [92, 93]. It is a phase 2/3, interventional, randomized, open-label trial to confirm whether it is feasible to identify and randomize patients with early septic shock to receive

Table 3 Ongoing studies in septic shock

	ARISS [89, 90]	**ALBIOSS-BAL [91]**	**SWIPE2 [92, 93]**
Country	**Germany**	**Italy**	**United Kingdom**
Number of patients	1662 (actual: 440)	1252	50
Study type	Prospective, multicenter, parallel-grouped, open-label, interventional RCT	2-by-2 factorial design, open-label, multicenter RCT	Multicenter, interventional, randomized, open-label, feasibility trial
Phase	3	3	2/3
Allocation arms	Albumin, crystalloids	Albumin + BAL, Albumin + NS, BAL, NS	Albumin, crystalloids
Intervention treatment	Loading dose: 60 g of HA 20% over 2–3 h Day 1–28: HA 20% to maintain albumin levels ≥ 30 g/L: ≥ 30 g/L: no administration 25–< 30 g/L: 40 g over 1–2 h 20–< 25 g/L: 60 g over 2–3 h < 20 g/L: 80 g over 3–4 h	Day 0–1: HA 20% 400 mL Day 2–90: HA 20% to maintain albumin levels ≥ 30 g/L	HA 20% guided by daily serum albumin values: ≥ 30 g/L: no administration 25–< 30 g/L: 20 g over 1–2 h twice daily 20–< 25 g/L: 20 g over 1–2 h three times daily < 20 g/L: 20 g over 1–2 h four times daily
Primary outcomes	90-day mortality	90-day mortality + new cases of AKI	to confirm feasibility of the study protocol
Status	Prematurely terminated	Enrollment completed July 2023 – last follow-up (90 days) Oct 2023	Recruiting

AKI acute kidney injury, *ALBIOS-BAL* ALBumin Italian Outcome Septic Shock Balanced Trial, *ARISS* Albumin Replacement therapy In Septic Shock, *BAL* balanced crystalloid solution, *h* hours, *HA* human albumin, *NS* normal saline, *RCT* randomized controlled trial, *SWIPE2* Strong Albumin Solutions in Patients With Septic Shock

albumin or crystalloids according to the study protocol [92, 93].

Conclusions

This review highlights the critical role of endothelial dysfunction in the pathogenesis of sepsis and the potential therapeutic benefit of albumin in this clinical context. The endothelium is significantly affected during sepsis, contributing to immune response activation, coagulation, and increased vascular permeability. Damage to the endothelial glycocalyx exacerbates these effects, leading to capillary leakage and organ dysfunction.

Treatment with adequate fluid resuscitation is associated with improved survival, as fluid overload is associated with worse outcomes. Human serum albumin, beyond its oncotic properties, offers several non-oncotic benefits such as antioxidant activity, transport and detoxification of compounds, modulation of immune responses, and stabilization of endothelial function. These properties make albumin a promising therapeutic agent in sepsis, with potential for improved outcomes if the correct patients can be targeted.

Although current evidence does not conclusively demonstrate a mortality benefit from albumin administration, particularly when compared to crystalloids, some studies suggest potential advantages in specific subgroups, such as patients with septic shock. Moreover, emerging data indicate that albumin may positively influence other clinical outcomes, including tissue perfusion, fluid balance, and hemodynamic stability. Reflecting this evolving evidence base, the Surviving Sepsis Campaign guidelines, increasingly cognizant of the potential benefits of albumin in the management of patients with septic shock, cautiously recommend the use of albumin in patients requiring large volumes of crystalloids.

These findings support the need for further targeted research to better define the patient populations most likely to benefit from albumin therapy and to clarify its role in modulating endothelial dysfunction. While several studies have been conducted or are ongoing—including ARISS, ALBIOSS-BAL, and SWIPE2—the results of the ARISS trial underscore the complexity of albumin therapy in septic shock and highlight the importance of identifying subgroups and endpoints beyond mortality to guide future clinical practice.

In conclusion, although preclinical studies suggest that albumin may exert beneficial effects on endothelial function, glycocalyx preservation, and microcirculatory stability, these mechanisms have not consistently translated into improved survival in large RCTs. Nevertheless, albumin remains a plausible therapeutic candidate, particularly in selected patient populations where its non-oncotic effects may offer clinical advantages. Further investigation is warranted to better define these subgroups and to clarify how albumin's non-oncotic properties—such as its antioxidant, anti-inflammatory, and endothelial-stabilizing effects—may contribute to mitigating sepsis-induced endothelial dysfunction and improving organ function beyond volume expansion alone.

Abbreviations

ARDS	Acute respiratory distress syndrome
EUR	Euros
ICAM-1	Intracellular adhesion molecule 1
ICER	Incremental cost–effectiveness ratio
ICP	Intracranial pressure
ICU	Intensive care unit
LYG	Life-year gained
MOF	Multiple organ failure
RCTs	Randomized controlled trials
SOFA	Sequential (or Sepsis-related) Organ Failure Assessment
TBI	Traumatic brain injury
US	United States
USD	United States dollars
VCAM-1	Vascular cell adhesion molecule 1
VEGF	Vascular endothelial growth factor

Acknowledgements

Irene Mansilla, MSc (Grifols) is acknowledged for medical writing and editorial support in the preparation of this manuscript.

Author contributions

IML: conceptualization, literature search, original draft, and editing. The rest of the authors revised and edited the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

Funding

This review article is based in part on a Grifols-sponsored symposium presented during the 35º smart meeting anesthesia resuscitation intensive care (SMART) 2024, May 31, 2024 in Milan, Italy. The publication of this review was funded by Grifols. Grifols provided editorial support in this manuscript by reviewing language style, format, and administrative assistance during the submission process. However, Grifols did not participate in the literature selection, interpretation, or presentation of the evidence. ACM is supported by an MRC Clinician Scientist Fellowship (MR/V006118/1).

Data availability

Not applicable. No datasets were generated or analyzed during the current work.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

IML, AR, LR, and SE declare that they have no competing interests. MSC has received speakers' fees from Edwards Lifesciences, Philips Healthcare and AOP Health. ACM sits on the scientific advisory board of Cambridge Infection Diagnostics and has received speaking fees from Thermo-Fisher, Biomerieux, Fischer and Paykel and Boston Scientific. ML served as a speaker for Viatris, Shionogi and Grifols and as a consultant for AOP Pharma, Biomerieux and Previa.

Received: 18 September 2025 Accepted: 9 November 2025
Published online: 27 November 2025

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